

Complementary and Alternative Medicine

Focus on Research and Care

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The Art and Science of Natural Products

Among the complementary and alternative medicine (CAM) approaches used by Americans, natural products are the most popular. Shelves at health food stores and supermarkets are full of natural products that claim to improve health. But what do we know about their claims of benefit? And are these "natural" remedies safe and do they work?

NCCAM-funded investigators are studying safety and probing whether and how natural products might affect health, including three that have attracted public interest and show scientific promise—fish oil, cranberry juice, and probiotics.



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An herbalist prepares a custom compound
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U.S. DEPARTMENT OF HEALTH
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Ginkgo Study Yields Insights for Treatment and Research

Recent estimates are that more than 5 million Americans have Alzheimer's disease, the most common age-related dementia. Past the age of 65, the number of people with Alzheimer's doubles every 5 years. As the population of the United States ages, interest is high in finding approaches, including from complementary and alternative medicine, that could prevent, slow the progression of, and treat cognitive impairments of aging.



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Ginkgo biloba

Could a CAM Remedy Help?

After its founding in 1999, NCCAM sought to advance knowledge on the safety, efficacy, tolerability, and acceptability of a short list of

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Fish Oil and Omega-3s

More than 30 years ago, researchers noticed that Eskimos have a low incidence of heart attacks, even though their diet relies heavily on whale blubber. Was there something about the fat-laden food that was protective? Perhaps the chemical nature of the fat?

Researchers investigated and found that the fat in whale blubber with its high content of omega-3 fatty acids (omega-3s) differed from fat in a conventional Western diet. Omega-3s are polyunsaturated fatty acids found in many foods (fish, fish oil, some vegetable oils, walnuts, and wheat germ) and also available as dietary supplements. The most important source of omega-3s is in food, particularly fish. But the supplements are the hot sellers. Fish oil and omega-3

supplements are the most commonly used natural products, taken by 37 percent of U.S. adults who use such products.

In spite of high public interest in omega-3s, there are still unanswered questions about the effects of changing fatty acid intake through diet or by taking dietary supplements, even for cardiovascular disease where the research picture is the best developed. A recent meta-analysis concluded that omega-3 supplementation for a year or longer appeared to be beneficial, for example, in reducing risk for cardiovascular deaths and overall mortality. The analysis included 11 studies with more than 39,000 patients who had recently survived a myocardial infarction, had an implanted cardioverter defibrillator, or had heart failure or other cardiovascular disease.

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Possible Benefits of Foods

The foods we eat are also rich sources of a variety of potentially beneficial molecules, from essential fatty acids to antioxidants to a wide array of other phytochemicals (chemicals found in plants). In fact, modern epidemiology research has revealed a number of connections, or correlations, between intake of specific kinds of food—fruits, vegetables, nuts, fish, even red wine—and overall good health. For example, observational studies suggest that eating a diet high in antioxidant-rich vegetables and fruits is associated with a lower risk for many chronic diseases. However, attempts to produce similar results with dietary supplements have often not shown the same results. Thus the continued need for basic and clinical research.



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Setting Priorities for Research on Natural Products

As part of our year-long strategic planning effort, we are thinking critically about our research into CAM natural products—including herbal medicines and other nonvitamin, nonmineral dietary supplements.

Since NCCAM began its research on natural products more than a decade ago, we have supported more than 2,500 investigator-initiated projects at academic research centers around the country, with more than half dealing with natural products. Many of the natural products studies have yielded fascinating science and high-quality publications.



In this Director's message, I want to focus on a special part of our natural products portfolio, the small number of signature projects done in partnership with other NIH institutes and centers—the large

From the Director

randomized, double-blind clinical trials of dietary supplements. These signature projects carry some important "lessons learned."

These studies were all implemented by leading investigators around the country and most had the benefit of generous product support and expertise from leading supplement manufacturers. All these studies were designed to meet the highest standards of excellence in clinical research and to provide results that could inform health practice recommendations. Products studied included St. John's wort for depression, ginkgo for dementia, glucosamine and chondroitin for arthritis, and vitamin E and selenium to prevent prostate cancer.

Because many people were already using these products, NCCAM's leaders and our partners at NIH felt there was some urgency to learn whether they worked and if they were safe. The studies were begun with high hopes. In all of these major trials, there was a substantial body of clinical data suggesting efficacy. Nonetheless, with some exceptions, benefits of the products could not be demonstrated. So these results were, in some respects, both surprising and disappointing.

Certainly, the absence of benefit of the products, as studied, was an important result, and these studies appear to have had major impact on patterns of public use. They have also clarified important safety issues. And for some of these products, there are still things to learn.

The completed research also carries lessons for the next generation of studies. We have learned about the steps of quality product characterization, and the critical value of mechanistic underpinning to make trials, positive or negative, maximally informative. We have learned that we need to develop very sensitive trial designs that will minimize the placebo effect. Large improvement in the control arm, in patients receiving the inactive (placebo) preparation, is also a fact in pharmaceutical trials, but is perhaps even more important with the kind of gentle interventions represented by CAM natural products.

So—where do we go from here?

In our scientific inquiries, we need to understand both efficacy and mechanism. We have learned that the design of maximally informative efficacy studies requires mechanistic insight. In discussing the framework to prioritize what studies to undertake, four primary factors come into play:

- **Science:** Is there clear scientific opportunity in studying this product or practice? Are there methods and technologies available that permit rigorous studies to clarify biological mechanism and ultimately clinical efficacy?
- **Promise:** Is there a body of evidence indicating that the product or practice has the potential to contribute to treating troublesome or prevalent health conditions or symptoms? Or is there evidence it acts on a biological pathway of importance in health and disease?
- **Use:** Is the natural product or CAM practice in widespread use? Does the research address a public health concern regarding efficacy, safety, or lack thereof?
- **Impact:** Will the research have scientific or public impact?

As we move forward, we will place heightened emphasis on both discovery and development of promising CAM approaches that have the potential to affect consumer health practices and give health care providers the evidence-based information they need to best serve patients.

Josephine P. Briggs, M.D.
Director

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But the results of research to date don't necessarily mean that omega-3s are good for all types of heart ailments. For example, NCCAM grantee Gea-Ny Tseng, Ph.D., at Virginia Commonwealth University would like to know why omega-3s appear to protect those who've had a recent heart attack, but add vulnerability for patients at risk for ventricular tachycardia or fibrillation. To address some of these apparent contradictions for heart health, Dr. Tseng is studying the cellular and molecular



Omega-3 capsules

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Omega-3s in Fish

Today, the American Heart Association recognizes omega-3s found in fish as beneficial for the hearts of healthy people, those at high risk of—or who have—cardiovascular disease, and those who need to lower triglycerides. However, not all fish may be created equal when it comes to omega-3 content. NCCAM-supported researchers at Wake Forest University studied the fatty acid content in commonly eaten fish and found a wide range of omega-3 content. When the researchers focused on the four most commonly farmed fish, they found high levels of omega-3s in trout and Atlantic salmon but low levels in the increasingly popular tilapia and catfish. According to the researchers, these results raise questions about the influence of fish farming in changing the pattern of consumption of key fatty acids known to affect human health.

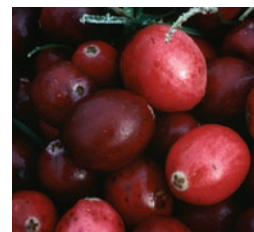
mechanisms by which fish oil supplements can affect the electrical activity of the heart, using animal models. She's found variations across species in how omega-3s affect the channels that conduct electricity to pump the heart, which may help explain why patients react differently to fish oil supplements.

Because omega-3s appear to affect many cellular functions beyond the heart, NCCAM and other NIH institutes also fund research on omega-3s in a variety of other areas, such as Alzheimer's disease, different forms of depression, eye health, metabolic disorders, and type 2 diabetes. For example, there is evidence that omega-3s may promote eye health. Animal studies and human epidemiology indicate a lower risk for macular degeneration with the use of omega-3s, and interventional studies are under way to test this promising possibility. There have also been reports from small studies that omega-3s modulate immune responses and decrease inflammation, with possible improvement in rheumatoid arthritis. And, two 2006 reviews of research on omega-3s for depression found support for the use of omega-3s as a supplement to standard care; the authors called for more research, including studies to determine mechanisms by which the supplements might influence emotional health.

For these potential omega-3 applications, many research questions remain. How do we best assess dietary fatty acid intake? Does it matter how omega-3s are provided—in the diet versus dietary supplements? In 2010, NCCAM and other NIH institutes hope to convene a working group to hear expert opinion on these and other important questions to determine research directions.

Cranberry Juice

In 2000 in the United States, urinary tract infections (UTIs) in adults accounted for about 11 million outpatient visits, 1.7 million emergency room visits, and \$3.5 billion in health care expenditures. UTIs are more common in women than men, and many women who have one UTI will have another. Cranberry juice is a popular UTI home remedy, and studies are showing that its popularity may make sense.



Cranberry

© Steven Foster

"The body of evidence [for cranberry] is growing to hopefully support popular belief," says Deborah Wing, M.D., an NCCAM-supported researcher at the University of California, Irvine. NCCAM and other NIH components support studies investigating cranberry's potential health benefits and biological effects in both UTIs and dental health.

One of four phase II trials has been published on cranberry and UTIs, and more are on the way, says NCCAM program officer Carol Pontzer, Ph.D. "They aren't large trials yet, but these intermediate-level trials are all suggesting it's worth going forward with larger studies."

For example, Dr. Wing's first study of cranberry to prevent UTI in pregnancy showed a trend toward reduction of asymptomatic bacteriuria (ASB) in pregnant women who drank cranberry juice multiple times per day. ASB is linked to preterm delivery and low birth weight. "Any measure that can reduce the frequency of ASB should translate into measurable improvement for birth outcomes overall," she explains. Her group is planning a larger, confirmatory study. But first they are working on a larger study to test the safety, compliance, and

tolerability of cranberry capsules, after the women in the initial study had trouble drinking enough cranberry juice (those who drank juice only once a day had much less benefit).

Cranberry contains a number of small molecules with potential beneficial effects such as polyphenols and proanthocyanidins. Laboratory studies suggest a number of interesting ways molecules in cranberry juice might have relevant biological effects. One possibility is that they bind iron, and the bacteria that cause infections of the urinary tract need iron to grow and multiply. Another possibility is that they interfere with bacterial adherence. The commonest cause of urinary tract infections is the bacteria *Escherichia coli* (*E. coli*). *E. coli* have finger-like structures on their surfaces called fimbria, and persistence of urinary tract infections seems to depend upon the binding of these fimbria to cells that line the bladder. Studies suggest that adherence of *E. coli* to bladder cells may be blocked by proanthocyanidins in cranberry juice.

A research group at the University of Rochester Medical Center, supported by the National Institute of Dental and Craniofacial Research, is studying the possibility that cranberry may be useful against tooth decay by blocking biofilm formation and acid production by bacteria found commonly in the mouth. Their research also suggests which specific compounds within cranberry juice—proanthocyanidins and flavonols—are active against the mouth bacteria *Staphylococcus mutans*.

In addition to understanding the biological effects of components of cranberry, NCCAM-funded researchers are also looking at safety and drug interactions. One recent study suggests that cranberry juice consumed in usual amounts does not interfere with two antibiotics often prescribed for UTIs.

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An Interview with Craig Hopp, Ph.D.

Pharmacognosist Craig Hopp, Ph.D., is a program officer in NCCAM's Division of Extramural Research, overseeing a research grant portfolio that covers a wide range of botanicals, including the NIH Botanical Research Centers Program. As a program officer, Dr. Hopp works with current and potential grantees to provide guidance regarding NCCAM research interests, priorities, and funding opportunities. Dr. Hopp received his B.S. in chemistry from James Madison University and his Ph.D. in natural products from Purdue University.



Photo credit: NCCAM

Craig Hopp, Ph.D.

What brought you to NCCAM?

I'm a natural products chemist by training, and I worked in industry for the last 10 years or so in natural products for pharmaceutical development. The level of interest in the pharmaceutical community for natural products research has decreased over the last 10 years, but the dietary supplement industry is actually growing by leaps and bounds. In trying to think about where it was that I could best utilize my skills and perhaps have the greatest impact, this position at NIH was extremely attractive to me.

Can you tell us about pharmacognosy and some of the challenges in this field?

The actual translation of pharmacognosy is the study of the medicinal uses of plants. Plant extracts are extremely complex, and trying to get the single useful compound out of the plant for a pharmaceutical purpose is a very difficult, time consuming, and expensive proposition.

Where do you believe the promise in the field is currently?

One of the things that natural-products, botanicals, and herbals advocates always point to is the fact that the complex product can give you benefits that you can't get by taking the individual components. This concept of synergy underlies

the beliefs of the herbal and botanical communities. And, this concept is scientifically plausible, but more research is needed.

What are some aspects of your portfolio?

One part of my grant portfolio is the botanical research centers. The concept of the center is that you have a relatively large group of people working on the same problem from different angles, and you have the potential to have major breakthroughs when you approach things in that way. The centers are also a major component of NCCAM's investment in botanicals and herbals.

Do you have any advice for consumers who use over-the-counter natural products?

Be careful. Although many dietary supplements (and some prescription drugs) come from natural sources, "natural" does not always mean "safe." There are examples of products where the content did not match the label in terms of what's in the product. And, if the claims sound too good to be true, they probably are. As we always mention at NCCAM, be an informed consumer, look for scientific research findings on the product in which you are interested, and talk to your health care providers.

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Probiotics and the Human Microbiome

In the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. The Human Microbiome Project is an NIH project exploring the bacterial flora that live in all of us, with the mission of generating resources to characterize human microbiota and analyze their role in health and disease. One exciting implication of this research will be improved understanding of a large category of natural products called probiotics, which may affect health by altering the microbial environment in the body.

The World Health Organization and the Food and Agriculture Organization of the United Nations define probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.” Probiotic foods and supplements are becoming increasingly popular in the United States. The most common types of probiotics used in food and dietary supplements are *Lactobacilli* and *Bifidobacteria*. Yogurt and other fermented foods are the main sources of naturally occurring probiotic bacteria.

Probiotics may have a wide array of potential clinical applications—preventing or treating problems ranging from gastrointestinal disorders to skin conditions to tooth decay. Researchers are working on many fronts to explore how probiotics might help to address important issues for promoting global health. For example, there is strong evidence of a beneficial role for probiotics against severe forms of diarrhea in children and infants (including necrotizing enterocolitis, a life-threatening condition in preterm infants).

NCCAM is collaborating with NIH’s Office of Dietary Supplements and the U.S. Food and Drug Administration’s Center for Food Safety and Nutrition to conduct an evidence-based review on probiotic safety. The analysis will catalog what is known about safety of probiotics being used; assess the quality and completeness of information; and provide recommendations, tools, and other resources for research.



Lactobacillus acidophilus; a spirochete bacterium is at center

NCCAM-supported researchers are examining whether there are potential benefits of probiotics through studies that seek to alter the gut microbial environment. Investigators are looking at several conditions including Crohn’s disease, ulcerative colitis, and antibiotic-associated diarrhea. For example, gut microflora are important contributors to disease in hepatic encephalopathy, a serious complication of cirrhosis of the liver. A small trial of 25 patients demonstrated significant improvement of hepatic encephalopathy with probiotic yogurt. A larger trial is planned.

Another area of active investigation is the effects of probiotics on the upper respiratory tract. Patricia L. Hibberd, M.D., Ph.D., chief, Division of Global Health, Massachusetts General Hospital for Children, says, “I’m particularly interested in understanding the normal respiratory microbiota and when and how it is perturbed by the presence of drug-resistant organisms.

These organisms can colonize the mucosal surfaces of the respiratory tract and may cause pneumonia or other invasive infections.” She continues, “We also want to find ways to prevent and eradicate colonization with these hard-to-treat bacteria that occur in many frequently hospitalized patients.”

Researchers are also looking at the developing world where diarrheal diseases are serious causes of morbidity and mortality, especially among young children. Rotavirus is the most common cause of severe dehydrating diarrhea in infants and children worldwide. In an animal study, researchers found that giving probiotics along with rotavirus vaccine boosted immune response to the vaccine. Thus, probiotics may offer a safe way to increase the effectiveness of rotavirus vaccine.

“The idea of trying to restore a healthy microflora in young children so they don’t get so many episodes of pneumonia and diarrhea would be huge,” says Dr. Hibberd. But probiotics would need to be inexpensive and able to prevent disease. “We have quite a long way to go before we will know whether probiotics could achieve these goals overseas.”

Dr. Hibberd has high hopes about the impact the NIH Human Microbiome Project will have on probiotics research. “We’re in the infancy of trying to understand the human microbiome,” says Dr. Hibberd. “One of the things that has made my research more interesting and relevant is that NCCAM [funding] is allowing me to study the effects of probiotics on the microbiome.”

References for this article are available at nccam.nih.gov/news/newsletter/2010_may/naturalproductrefs.htm.

Get the Facts

Information for Consumers

NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Antioxidant Supplements for Health: An Introduction



Natural antioxidants come from foods, including carrots, tomatoes, grain cereals, citrus, teas, and nuts.

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES

National Institutes of Health



Antioxidants are substances that may prevent potentially disease-producing cell damage that can result from natural bodily processes and from exposure to certain chemicals. There are a number of different antioxidants found in foods and available as dietary supplements. This fact sheet provides a general overview of antioxidants—with a focus on dietary supplements—and suggests sources for additional information.

Key Points

- People take antioxidant supplements in an effort to improve their health and to prevent various diseases. Examples of commonly used antioxidant supplements include vitamins C and E, selenium, and beta-carotene.
- Although observational studies suggest that eating a diet high in antioxidant-rich vegetables and fruits is associated with a lower risk for many chronic diseases, there is limited evidence to support the use of antioxidant supplements to prevent disease. Additional research, including studies supported by the National Center for Complementary and Alternative Medicine (NCCAM) and other components of the National Institutes of Health (NIH), is under way.
- Tell all of your health care providers about any complementary and alternative practices you use, including antioxidant supplements. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care.

About Antioxidants

Oxidation—one of the body's natural chemical processes—can produce “free radicals,” which are highly unstable molecules that can damage cells. For example, free radicals are produced when the body breaks down foods for use or storage. They are also produced when the body is exposed to tobacco smoke, radiation, and environmental contaminants. Free radicals can cause damage, known as “oxidative stress,” which is thought to play a role in the development of many diseases, including Alzheimer's disease, cancer, eye disease, heart disease, Parkinson's disease, and rheumatoid arthritis. In laboratory experiments, antioxidant molecules counter oxidative stress and its associated damage.

The body can produce its own antioxidants and also obtain them from food. Antioxidants are abundant in vegetables and fruits and are also found in grain cereals, teas, legumes, and nuts. Examples of antioxidants include anthocyanins, beta-carotene, catechins, coenzyme Q10, flavonoids, lipoic acid, lutein, lycopene, selenium, and vitamins C and E. Many antioxidants are also available as dietary supplements.

Although antioxidant molecules counter oxidative stress in laboratory experiments, there is some debate as to whether consuming antioxidants—in food or supplement form—actually benefits health. Antioxidant supplements are often synthetic (man-made), but some of

these synthetic forms may not have the same effects on the body as antioxidants that occur naturally in foods. In addition, some beneficial properties may be lost when antioxidants are extracted from foods to manufacture supplements. There is also some concern that consuming antioxidants in excessive doses may have negative effects.

Use of Antioxidant Supplements in the United States

In the National Health and Nutrition Examination Survey (NHANES, 1999-2000), over 5,000 of the approximately 10,000 respondents (52 percent), reported taking a dietary supplement in the previous month. Of the 1,900 dietary supplements included in the survey, more than 900 (47 percent) contained an antioxidant: vitamin C, vitamin E, beta-carotene, selenium, flavonoids, or isoflavones. More than 3,000 of the respondents (37 percent) reported taking dietary supplements that contained one of the antioxidants mentioned.

A 2009 study looked at data from NHANES (1999-2000 and 2001-2002) and the U.S. Department of Agriculture Flavonoid Database to estimate the total antioxidant intake (from diet and supplements) of adults in the United States. The researchers calculated the daily intake of vitamin C, vitamin E, carotenes, selenium, and flavonoids. They found that supplements accounted for 54 percent of vitamin C; 64 percent of vitamin E (alpha-tocopherol); 14 percent of carotenes; 11 percent of selenium; and 2 percent of flavonoid intake.

Status of Research on Antioxidant Supplements

There is limited scientific evidence to support the use of antioxidant supplements to prevent disease. Observational studies (which track a group of people without changing

their activities or providing special treatments) have shown that a higher intake of antioxidant-rich vegetables and fruits is associated with a reduced risk of certain chronic diseases. It is not clear, however, that the benefits are due to the antioxidants. Although observational studies, as well as laboratory research on the biochemistry of antioxidants, suggest that antioxidant supplements may have beneficial effects, clinical trials (controlled studies in people) have generally found no benefit.

Systematic reviews of the research literature have analyzed the use of antioxidant supplements for preventing cancer, cardiovascular disease, and eye disease, and reducing overall mortality in healthy people and people with various diseases. In general, these reviews have concluded that there is not enough evidence to support the use of antioxidant supplements for these purposes.

Large, long-term studies (randomized, controlled trials) funded primarily by NIH have generally found that antioxidant supplements have no beneficial effects. For example:

- The Physicians Health Study II, which included more than 14,000 healthy male physicians aged 50 or older, found that neither vitamin E nor vitamin C supplements reduced the risk of major cardiovascular events (e.g., heart attack, stroke, or death) or cancer.

- The Selenium and Vitamin E Cancer Prevention Trial (SELECT)—a study of more than 35,000 healthy men aged 50 or older—found that selenium and vitamin E taken alone or together did not prevent prostate cancer. (Two earlier reviews suggested that preliminary evidence for selenium appeared promising).

- The Women's Health Study, which included almost 40,000 healthy

women at least 45 years of age, found that overall, vitamin E did not reduce the risk of death, major cardiovascular events (e.g., heart attack, stroke, or death), or cancer. However, it was associated with reduced deaths from cardiovascular causes and also reduced major cardiovascular events in a subgroup of women aged 65 or older.

- The Women's Antioxidant Cardiovascular Study found no beneficial effects of vitamin C, vitamin E, or beta-carotene on cardiovascular events (e.g., heart attack, stroke, or death) in more than 8,000 female health professionals, aged 40 years or older, who were at high risk for cardiovascular disease.

An important exception to this trend is a National Eye Institute study of age-related eye disease, which found that the combination of antioxidants and zinc reduced the risk of developing advanced stages of age-related macular degeneration (AMD) by 25 percent in people who had intermediate AMD or advanced AMD in only one eye. Antioxidant supplements used alone reduced the risk by about 17 percent.

Thus, despite widespread scientific interest and clear plausibility of benefit, the body of evidence for antioxidant supplements has not, to date, demonstrated substantial health benefits. Additional research, some of it aimed at understanding the "disconnect" between findings of laboratory and observational studies and results of clinical trials, is under way.

Safety

Antioxidants in foods are generally considered safe, and studies of antioxidant supplements generally have not reported adverse effects. However, the research does point to some potential concerns; for example, beta-carotene supplements may increase the risk of

lung cancer in smokers, and vitamin E supplements may increase the risk of bleeding in certain individuals. More research is needed to better understand the safety aspects of dietary supplementation. For more information about dietary supplements, see the NCCAM fact sheets *Using Dietary Supplements Wisely* and *Are You Considering CAM?*



Many antioxidants are sold as dietary supplements

If You Are Thinking About Using Antioxidant Supplements

- Do not use antioxidant supplements as a replacement for a healthful diet or conventional medical care, or as a reason to postpone seeing a doctor about a medical problem.
- Consult your health care provider before deciding to use antioxidant supplements.
- Look for published research studies on antioxidant supplements for the health condition that interests you.
- Tell all of your health care providers about any complementary and alternative practices you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care. For tips about talking with your health care providers about complementary and alternative medicine (CAM), see NCCAM's Time to Talk campaign at nccam.nih.gov/timetotalk/.

NCCAM-Funded Research

Because antioxidants are widely used, and because there is laboratory and observational evidence of potential health benefits, antioxidants are the subject of extensive research across NIH, including recent NCCAM-sponsored studies that have been investigating:

- Three antioxidant regimens—**Ginkgo biloba**, **alpha-lipoic acid/essential fatty acids**, and **vitamin E/selenium**—as potential treatments for multiple sclerosis
- **Lipoic acid**, an antioxidant used in the treatment of diabetic neuropathy, to improve blood vessel reactivity and decrease oxidative stress

in people with high cholesterol

- The safety of the vitamin E supplement **gamma-tocopherol** in healthy people and those with asthma and allergies
- The combination of **vitamins E and C** to enhance airway antioxidant levels in people with allergic asthma and reduce the incidence of preeclampsia among pregnant women with chronic hypertension or a history of preeclampsia/eclampsia
- **Alpha-lipoic acid** and fish oil to slow the progression of Alzheimer's disease
- Whether **alpha-tocopherol** (vitamin E) supplementation affects the progression of carotid atherosclerosis (narrowing or hardening of the carotid artery) in patients with coronary artery disease
- The safety and efficacy of **vitamin E** in slowing the rate of cognitive and functional decline in older persons with Down syndrome.

NCCAM also funds two research centers that are studying the effects of antioxidants on aging, amyotrophic lateral sclerosis (ALS, commonly known as Lou Gehrig's disease), asthma, and cardiovascular diseases.

Other NIH studies on antioxidants have been investigating:

- The effects of **vitamin C** on the lung development and function of babies born to women who smoke during pregnancy
- Whether an antioxidant drug (**n-acetylcysteine**) taken orally will improve glucose tolerance and insulin secretion in type 2 diabetic subjects
- The safety and effectiveness of **coenzyme Q10** (combined with **vitamin E**) to slow the progression of Parkinson's disease
- The side effects and best dose of **high-selenium Brassica juncea** (mustard plant) and capecitabine (a cancer drug) given together with irinotecan (a cancer drug) as a treatment for patients with advanced cancer
- Whether antioxidants (**beta-carotene**, **vitamin C**, and **vitamin E**) combined with magnesium can prevent noise-induced hearing loss.

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For More Information

You can learn more about antioxidants from NCCAM by viewing the expanded version of this fact sheet at nccam.nih.gov/health/antioxidants/ or ordering a printed version from the NCCAM Clearinghouse. The expanded fact sheet includes additional resources.



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The NCCAM Clearinghouse provides information on CAM and NCCAM, including publications and searches of Federal databases of scientific and medical literature. Please note that NCCAM does not provide medical advice, treatment recommendations, or referrals to practitioners.

Correction

In the "Colds and Flu: Can CAM Help?" article in the "Get the Facts" section of the February 2010 issue, the box entitled "Fighting Colds With CAM" incorrectly labeled *Andrographis paniculata* with the common name of South African geranium. The correct common name is andrographis. South African geranium is a common name for *Pelargonium sidoides*, also known as umckaloabo.



NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
National Institutes of Health U.S. Department of Health and Human Services

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CAM therapies being widely used by Americans. The new Center funded a number of large randomized clinical trials of natural products: glucosamine (for degenerative arthritis of the knee), saw palmetto (for urinary symptoms in men with enlarged prostates), St. John's wort (for major depression), and *Ginkgo biloba* (for dementia and cognitive decline in older people).

This article discusses the ginkgo study, which illustrates the challenges of studying a natural product and the lessons that NCCAM has learned about product integrity, reproducible results, and the role of CAM in addressing a condition with a high public health burden.

Why Ginkgo?

People use ginkgo leaf extracts hoping to improve memory; to treat or help prevent Alzheimer's disease and other types of dementia; to decrease intermittent claudication (leg pain caused by narrowing arteries); and to treat sexual dysfunction, multiple sclerosis, tinnitus, and other health conditions.

Richard Nahin, Ph.D., M.P.H., the NCCAM program officer for the ginkgo

study, explains the scientific rationale for studying ginkgo: "At the time, there was a reasonable amount of preclinical data and some small clinical trials suggesting the potential value and a plausible scientific case that ginkgo might be neuroprotective. That is, there was preliminary data suggesting that ginkgo had antioxidant, free-radical-scavenging, anti-inflammatory, and/or pro-circulatory properties. However, there was a need for an adequately designed and powered clinical study to obtain a definitive answer about whether ginkgo offers neuroprotection against age-related dementia."

Steven T. DeKosky, M.D., then head of the Alzheimer's Disease Research Center and chair of the Department of Neurology at the University of Pittsburgh, undertook the study. A physician trained in behavioral neurology, neurochemistry, and



Data from the Ginkgo Evaluation of Memory study are yielding insights on the health of older people

molecular neurobiology, DeKosky was interested in brain-body diseases.

"Ginkgo interested me because of its antioxidant properties; the fact that it has 'been around' for over 1,600 years; and its use for cognitive preservation," he says. "We saw that ginkgo had biological activities that made sense in terms of what we know today about Alzheimer's disease. I think that anyone who comes into this work through neurological training and clinical care (e.g., of cognitive impairments, seizures, gait disorders, depression, or back pain) encounters CAM and patients using CAM."

In 2008, the primary results from DeKosky's study, titled the Ginkgo Evaluation of Memory study, were published in *JAMA: Journal of the American Medical Association*. The study found that ginkgo, as used in an older population, did not prevent the emergence of either Alzheimer's or dementia from other causes. A second paper, also published in *JAMA* in 2009, did not find ginkgo helpful for age-related memory decline.

"These were not the results we had hoped for," Dr. DeKosky says. "They confirm, however, the importance of randomized controlled trials in the

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More About the Ginkgo Evaluation of Memory Study

- A formulation of 120 milligrams of ginkgo, compared with an identical placebo, was taken twice daily. Schwabe Pharmaceuticals provided the product and placebo.
- The primary outcomes of the study were the incidence of dementia generally, and Alzheimer's disease specifically, according to DSM-IV criteria and confirmed by MRI scan as to type.
- The participants—3,069 community-dwelling people aged 75 and older— included a group with normal cognition and a group with mild cognitive impairment. They were followed for an average of 5.8 years.
- Funding for the study came from NCCAM, the National Institute on Aging, the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the NIH Office of Dietary Supplements.

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development of new therapies for dementia and Alzheimer's disease and in determining therapeutic benefit not only for conventional therapies but for CAM therapies like ginkgo."

Benefits Beyond the Results

While the primary results were disappointing, the study did yield a substantial body of useful information. "Among other benefits," Dr. DeKosky says, "we showed that you can do a large-scale, classic randomized controlled trial—one that also follows FDA's results criteria—in this older age group, and have the participants remain in the trial long enough to get a clear answer."

"In addition, we obtained a tremendous body of fascinating information on the older population, and there is more to come," he continues. "As people have come out of our study at an average age of 85, we are doing an extra test on 400 participants. We want to see what the brains of very old people who are cognitively normal look like from an atrophy or stroke standpoint. Science doesn't have much data on the 'oldest old.'"

Selected participants at the Pittsburgh study site are receiving a new type of PET tracer called the Pittsburgh Compound B (PiB), which Dr. DeKosky says appears to provide a good measure of amyloid plaque deposits. [These deposits, found in the space between nerve cells in the brain, are a feature of Alzheimer's; see scans in box at right.]

"The new data should help us with questions such as: how many normal 85-year-old people have these plaques and thus have Alzheimer's, but are not affected by it? What happens over the next 5 years?" he says. "This is the kind of information needed in the field to develop new approaches to prevention,

testing, and treatment of Alzheimer's and the age-related dementias."

Dr. Nahin notes that the ginkgo study data should help in answering questions such as what factors may influence the onset of dementia or be protective against it: "Are they genetic, environmental, social, or other factors, such as other diseases? Is there any relation to healthy living?"

Other benefits gained from the ginkgo study include:

■ NCCAM worked with ginkgo supplement manufacturers to ensure a well-characterized and standardized herbal formulation to study. This rigorous quality control approach laid the foundation for NCCAM's Natural Product Integrity Process today. The process helps maximize the validity and

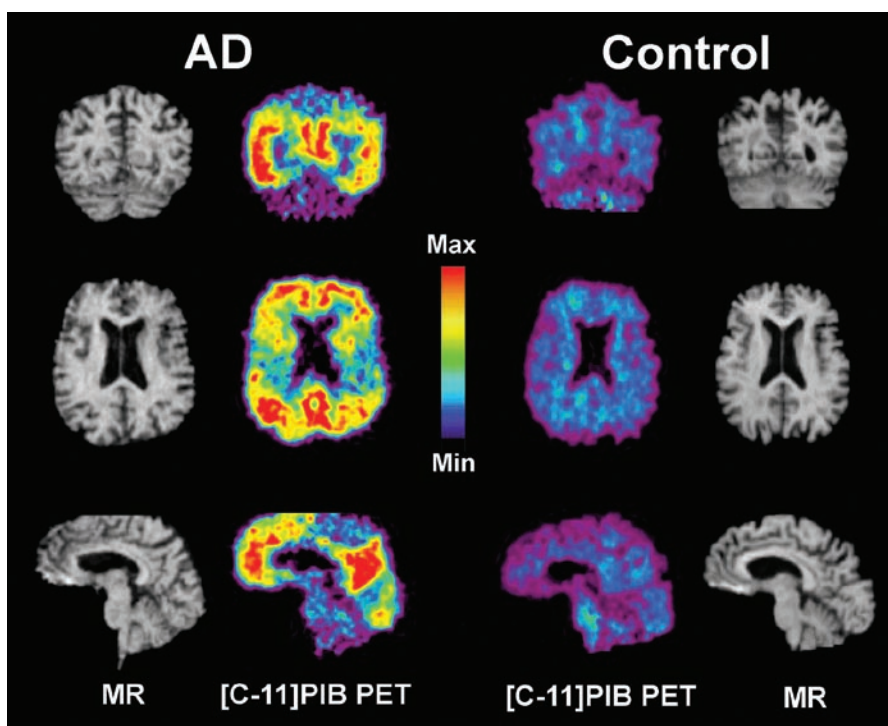


Image credit: University of Pittsburgh PET Amyloid Imaging Group. Used with permission.

Technology Helps Detect Early Alzheimer's

These 12 scans, of two participants of similar age in the Ginkgo Evaluation of Memory study, compare a brain with mild Alzheimer's disease to a brain of normal cognition. The black-and-white MRI scans at far left show only mild, age-appropriate brain atrophy (no changes characteristic of Alzheimer's). The color images in the left center column, from this same patient, show amyloid plaque deposits, a hallmark of Alzheimer's. Red, orange, and yellow show more to less density and intensity of plaque, respectively. The scans at right center and far right are from the second participant. They show mild, age-appropriate brain atrophy, but no colors indicating amyloid plaque deposits. The color scans used a radioactive dye called Pittsburgh Compound B (PiB) along with PET (positron emission tomography) scanning—a relatively new approach that can help diagnose early brain changes in Alzheimer's patients.

reproducibility of results from studies of natural products, which are inherently variable and can also be altered by outside factors.

- The study team is gaining insights about other health issues in the group of participants (see box at right).

- The study added to the safety profile of ginkgo, a supplement that is widely taken by the public. In the study, there were no significant differences in the adverse event profiles between ginkgo and the placebo with respect to risk for bleeding and gastrointestinal problems, common side effects with ginkgo products.

Leveraging Results

Insights from the ginkgo study and NCCAM's other early clinical trials using natural products are informing the Center's approach to natural

product studies in the future. "Our ginkgo study demonstrated that this well-characterized product, studied in the way (including dosage) that it is used in 'the real world,' did not help prevent age-related dementia or cognitive decline," says Josephine P. Briggs, M.D., Director of NCCAM. "This is important information for the public."

"As we consider future clinical studies of natural products, however, we know more about what elements we need to have in place for a high-quality study. These include scientific promise, early evidence, a strong scientific rationale, and a quality study design. Future trials will be stronger if we have insight on the product's possible mechanism of action and chemical properties. It is particularly valuable if we have markers of a biological effect that is related to the hypothesized mechanism of action. Advanced technologies, such as proteomics and gene expression methods, can help us fill these knowledge gaps. The traditional knowledge we have on the use of these products will continue to be valuable as well."

The communication about CAM between health care providers and their patients also remains critical, Dr. Briggs notes. One reason is that older patients, especially, very often take both drugs and supplements, and interactions can occur. "Open dialogue helps ensure safe and coordinated care," she says.

References

DeKosky ST, Williamson JD, Fitzpatrick AL, et al. *Ginkgo biloba* for prevention of dementia: a randomized controlled trial. *JAMA: Journal of the American Medical Association*. 2008;300(19):2253-2262.

Snitz BE, O'Meara ES, Carlson MC, et al. *Ginkgo biloba* for preventing cognitive decline in older adults: a randomized trial. *JAMA: Journal of the American Medical Association*. 2009;302(24):2663-2670.

For more references, go to [nccam.nih.gov/news/ newsletter/2010_may/ginkgostudyrefs.htm](http://nccam.nih.gov/news/newsletter/2010_may/ginkgostudyrefs.htm).

Talking with Patients About Ginkgo

Dr. DeKosky, who is now vice president and dean of the University of Virginia School of Medicine and serves on NCCAM's national advisory council, has patients who ask him about using natural products for their memory. He does not recommend them, he says, because of lack of proof that they work, and even in some cases lack of a plausible mechanism as to why they might work, for this purpose. However, for patients who want to try a supplement, he uses these general rules:

- Is it safe?
- Are there data to support use?
- Could it interfere with any of the medicines the patient is taking, whether for Alzheimer's or another condition?
- Is the cost reasonable enough that it would not be a hardship?

What Else Are We Learning from the Study?

Reports being published on many other health topics from the Ginkgo Evaluation of Memory data include:

- Cardiovascular health and hypertension
- Cancer risk
- Gait speed
- Thyroid function
- Blood pressure
- Personality
- Alcohol consumption
- Activities of daily living
- Overweight
- Use of herbal medicines and other dietary supplements together
- Use of specific types of medications.

To read abstracts of published reports, search PubMed at www.ncbi.nlm.nih.gov/pubmed.

NCCAM Exhibits at Upcoming National Meetings

- **June 23–27** American Academy of Nurse Practitioners, Phoenix
- **July 31–August 4** 2010 National Medical Association, Orlando
- **August 11–15** American Association of Naturopathic Physicians, Portland
- **August 12–15** American Psychological Association, San Diego
- **September 30–October 2** AARP, Orlando

Research Digest

Study Shows Chamomile Capsules Ease Anxiety Symptoms

Generalized anxiety disorder (GAD) has a wide array of psychological and physical symptoms. Although prescription drugs can help, they often have undesirable side effects. Many people experiencing symptoms of anxiety do not seek

to 1.2 percent of the constituent apigenin; or chamomile-scented placebo capsules containing lactose. The initial dose of one capsule daily was increased to two capsules daily at week 2; dosages were then adjusted incrementally (up to five capsules) in some participants. Researchers used the Hamilton Anxiety Rating (HAM-A) and other tests to measure changes in anxiety symptoms over the course of the study; dosage adjustments were

based on HAM-A scores.

Compared with placebo, chamomile was associated with a greater reduction in mean HAM-A scores—the study's primary outcome measure. The difference was clinically meaningful and statistically significant. Chamomile also compared favor-

ably with placebo on other outcome measures (although the differences were not statistically significant), and was well tolerated by participants.

These results suggest that chamomile may have modest benefits for some people with mild to moderate GAD. As this was the first controlled trial of chamomile extract for anxiety, the researchers note that additional studies using larger samples and studying effects for longer periods of time would be helpful. They also point out that other chamomile species, preparations (e.g., extracts standardized to constituents other than apigenin), and formulations (e.g., oil or tea) might produce different results.

Reference

Amsterdam JD, Yimei L, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. *Journal of Clinical Psychopharmacology*. 2009;29(4):378-382.

Additional Resources

Information on chamomile is available from NCCAM at nccam.nih.gov/health/chamomile/.

Information on GAD is available from the National Institute of Mental Health at www.nimh.nih.gov/health/topics/generalized-anxiety-disorder-gad/index.shtml.

Supportive Patient-Practitioner Relationships May Benefit Patients

Clinical trial data indicate that supportive interactions with health care providers can benefit patients and may be especially helpful for people who tend to be reclusive (keep to themselves). In a trial funded in part by NCCAM and published in *Social Science & Medicine*, participants with irritable bowel syndrome (IBS) who received placebo (simulated) acupuncture had some improvement in symptoms, but those who also received support from the acupuncture practitioner experienced even greater improvement.

Researchers from Harvard Medical School Osher Research Center and other Boston-area institutions randomly assigned participants with IBS to one of three groups: wait list (assessment and observation only), placebo acupuncture alone (minimal interaction with the practitioner), or placebo acupuncture plus supportive interaction with the practitioner (detailed questions, expressions of empathy, attentive listening, etc.). Simulated acupuncture alone yielded modest improvement of IBS symptoms, but when combined with



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Chamomile

medical attention, turning instead to alternatives. One traditional remedy in widespread use is the herb chamomile. However, scientific evidence to support the use of chamomile for anxiety has been lacking.

NCCAM-funded researchers at the University of Pennsylvania recently conducted a randomized, double-blind, placebo-controlled trial to test the effects of chamomile extract in patients diagnosed with mild to moderate GAD. For 8 weeks, the 57 participants received either chamomile capsules containing 220 mg of pharmaceutical-grade extract from *Matricaria recutita* (German chamomile), standardized



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supportive interaction simulated acupuncture brought significant improvement. Upon further analysis of participant characteristics (452 background, medical, psychological, and social factors for 289 participants) to see whether some participants benefited more than others from the supportive interaction, only two factors—reclusiveness and previous trial experience—stood out. (The analysis also suggested that participants who did not receive practitioner support benefited from getting a chance to talk about their experiences in an interview.) To sift through the many factors and ensure important results weren't inadvertently eliminated, this study used a statistical technique widely used in genomics research to test thousands of genes for links to diseases.

In light of these findings, the authors recommended additional research to explore the role of patient-practitioner interactions and other social factors in healing.

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NCCAM Portal Page on Dietary and Herbal Supplements

nccam.nih.gov/health/supplements/

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nccam.nih.gov/health/links/

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www.ncbi.nlm.nih.gov/sites/entrez

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Office of Dietary Supplements

Web site: www.ods.od.nih.gov
E-mail: ods@nih.gov

Dietary Supplements Labels Database

dietarysupplements.nlm.nih.gov/dietary

IBIDS (International Bibliographic Information on Dietary Supplements)

www.dietary-supplements.info.nih.gov/health_information/ibids.aspx

U.S. Food and Drug Administration

Web site: www.fda.gov
Toll-free in the U.S.: 1-888-463-6332

Federal Trade Commission

Web site: www.ftc.gov
Toll-free in the U.S.: 1-877-382-4357

Reference

Conboy LA, Macklin E, Kelley J, et al. Which patients improve: characteristics increasing sensitivity to a supportive patient-practitioner relationship. *Social Science & Medicine*. 2010;70(3):479-484.

Additional Resources

More information on this clinical trial is available from NCCAM at nccam.nih.gov/research/results/spotlight/040308.htm.

More information on IBS is available from the National Institute of Diabetes and Digestive and Kidney Diseases at www.digestive.niddk.nih.gov/ddiseases/pubs/ibs.

NCCAM Update, an e-bulletin of news from NCCAM, is now being sent twice per month. To subscribe, go to nccam.nih.gov/news/subscribe.htm.

On that page, you can also sign up for NCCAM on Twitter and/or the Center's RSS news feed.



The next meetings of the **National Advisory Council for Complementary and Alternative Medicine** will take place on **June 4** and **September 3, 2010**, in the Neuroscience Center Building, 6001 Executive Blvd., Rockville, Maryland. Agendas will be posted at nccam.nih.gov/about/naccam/.

Complementary and Alternative Medicine: Focus on Research and Care

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Improving Patient-Provider Communication

Increasingly, today's patients are playing an active role in their health care. Patients and their health care providers need to communicate clearly and work closely together to achieve the best possible level of health care. NIH and its components (including NCCAM) offer many publications to help promote clear, meaningful communication between patients and providers.

For links, visit "Talking to Your Doctor" at www.nih.gov/clearcommunication/talktoyourdoctor.htm.

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Resources from NIH

More and more, today's patients are playing an active role in their health care. Patients and doctors work closely together to achieve the best possible level of health care. An important part of this partnership is clear communication. Asking the right questions and obtaining quality information about prevention, diagnosis, treatment, and recovery help ensure safety, prevent errors, and improve health. For example:

- » Sharing questions about prescriptions with can prevent taking too much or too little medicine
- » Being honest about symptoms can help doctors order the right tests and make the right diagnoses
- » Clear instructions after an operation or hospital stay may be the difference between complete recovery or re-injury and relapse

Taking along a family member, friend or caregiver to help you communicate with your doctor can help. So can writing down your questions or concerns in advance of your appointment. NIH offers several publications that can also help promote meaningful interactions between patients and doctors.

How to Talk to your Doctor

- » *Preparing for Your Doctor Visit*, NIH News in Health
- » *Become a Partner in Your Health Care*, NIH News in Health

Cancer

- » *Communication in Cancer Care*, National Cancer Institute (NCI)
- » *Participating in a Trial: Questions to Ask Your Doctor*, National Cancer Institute (NCI)